Chapter 7

Hormone Secretion in Pituitary Adenomas: Immunohistochemical Studies

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Abstract

Classification of pituitary adenomas is still changing and not completely satisfying. Various types of hormones, prehormonal substances, and transcription factors are detected in pituitary adenomas. Monohormonal secretion in pituitary adenomas is frequent, notably prolactin secretion. Secretion of more than one hormone normally originating from the same adenohypophyseal cell lineage is well known, classically GH-PRL and FSH-LH. Other combinations of hormonal secretion are reported; they are sometimes underestimated. Plurihormonal secretion in pituitary adenomas, which is secretion of hormones that are normally originating from different adenohypophyseal cell lineages, is usually underestimated and in most cases remains subclinical. An immunohistochemical study of all pituitary hormones and prehormonal substances, as demonstrating transcription factors, is not always available; it is frequently not performed. This chapter aims to show the underestimated and vague areas of pituitary adenomas and to emphasize the importance of immunohistochemical studies in the diagnosis and prediction of clinical outcomes of these adenomas.

Keywords: pituitary adenoma, monohormonal adenoma, plurihormonal adenoma, atypical adenoma, aggressive adenoma, high-risk adenoma, pituitary neuroendocrine tumor, pituitary carcinoma, immunohistochemical studies

1. Introduction

Classification of pituitary adenomas is still changing; it requires morphological and hormonal immunohistochemical assessments. These adenomas reveal various histopathological patterns and tinctorial properties which proved to be unreliable and do not always correlate with the functional or immunohistochemical findings.

The 3rd WHO classification of pituitary adenomas [1]	The 4th WHO classification of pituitary adenomas [3]
Growth hormone producing adenoma	Somatotroph adenoma
Prolactin producing adenoma	Lactotroph adenoma
Thyrotropin producing adenoma	Thyrotroph adenoma
ACTH producing adenoma	Corticotroph adenoma
Gonadotropin producing adenoma	Gonadotroph adenoma
Null cell adenoma	Null cell adenoma
Plurihormonal adenoma	Plurihormonal and double adenoma

Table 1. Comparison between the 3rd and the 4th WHO classification of pituitary adenomas.

The 3rd WHO classification of adenohypophyseal cell lineage in pituitary adenomas in 2004 was based on functional properties using histological study, immunohistochemical properties, ultrastructural features, biochemical imaging, and surgical findings [1].

The 4th WHO classification of pituitary adenomas in 2017 [2] is mostly based on the adenohypophyseal cell lineage designation according to immunohistochemical markers such as pituitary hormones and pituitary-specific transcription factors. Comparison between the 3rd and the 4th WHO classification is shown in **Table 1**.

Some transcription factors and cofactors have a known role in the differentiation of pituitary cell lineages [2–4], e.g., PIT1 (pituitary transcription factor 1 for growth hormone also known as POUF1 [3]), ER-alpha (nuclear estrogen receptor alpha), SF1 (splicing factor 1), and TPIT (transcription factor for pituitary corticotroph cell lineage).

Many adenomas secrete one hormone; though secretion of more than one hormone is well documented, the following combinations of hormones are reported [1, 3]:

- GH (growth hormone) and PRL (prolactin)
- FSH and LH
- FSH, LH, TSH, and a-SU (alpha subunit is identical for gonadotropin hormones and TSH)

Tumor cells in these cases are originating from the same cell lineage.

2. Value of immunohistochemical studies in pituitary adenomas

Immunostaining is achieving a progressively important role in pituitary adenomas. The 4th WHO classification of pituitary adenomas in 2017 [2] is mostly based on the adenohypophyseal cell lineage designation according to immunohistochemical markers for the main secreting hormones; for example, the new designation "somatotroph adenoma" defines a group of tumors that are derived from a PIT1 lineage and secrete growth hormone; this replaces the former term growth hormone-producing adenoma as previously designed in the 3rd WHO classification [1].

Immunohistochemical markers allow for differentiation between clinically relevant histological subtypes that was mainly ultrastructural features. Electron microscopy is now rarely

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used to classify pituitary tumors; it is not necessary for the routine investigation of pituitary tumors. However, ultrastructural evaluation may be useful in the differential diagnosis of undifferentiated tumors and in a very limited number of adenoma subtypes, such as plurihormonal PIT1-positive adenoma [2].

Transcription factors for pituitary cell lineages are as follows [3, 4]:

- Somatotroph lineage: PIT1, which is a pituitary transcription factor 1 for growth hormone also known as POUF1.
- Lactotroph differentiation: PIT1 and ER-alpha.
- Thyrotroph differentiation: PIT1 and GATA2. GATA2 is a nuclear protein regulating gene expression.
- Gonadotroph differentiation: GATA2 and SF1. SF1 is splicing factor 1, also known as zinc finger protein 162.
- Corticotroph cell lineage: TPIT.

3. Plurihormonal pituitary adenomas

Plurihormonal pituitary adenomas are defined as tumors that show immunoreactivity for more than one hormone that cannot be explained by normal cytophysiology or developmental mechanism [5]. They can be monomorphous, consisting of a single cell type producing two or more hormones, or plurimorphous, consisting of two or more different cell lineages.

Plurihormonality is reported in the literature; it is estimated rare in most studied series while they are more frequent in other series [5, 6–8]. Most plurihormonal adenomas are silent [2]. Various combinations are described in the literature in the studied series:

- PRL and LH; PRL and TSH [7]
- GH and ACTH [9–11]
- PRL and ACTH [5, 7, 12, 13]
- ACTH, LH, and TSH [7]
- PRL, LH, FSH, and TSH [7]
- GH, PRL, TSH, and a-SU [5]
- GH, PRL, and ACTH [7, 14]
- GH, PRL, TSH, FSH, and aSU [15]

Other less common combinations are also published [5]. Original examples of plurihormonal adenomas in the author series [7] are shown in **Figures 1–3**.

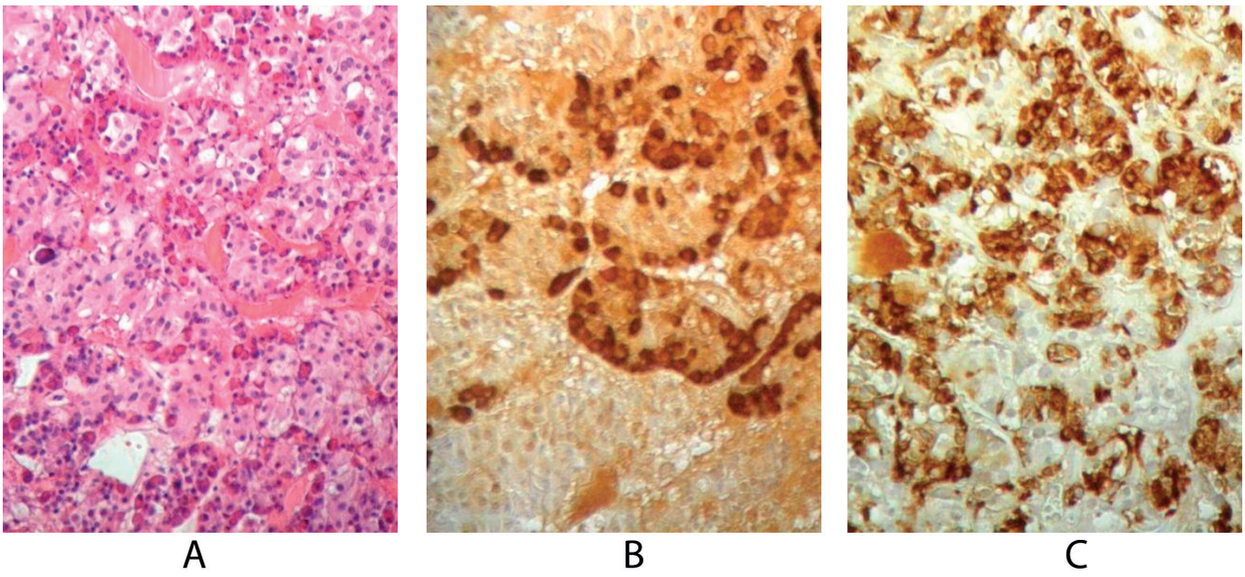

Figure 1. (A) Pituitary adenoma revealing a trabecular and nested structure (HE stain, x200), composed of two distinct types of cells. (B) ACTH secretion in the same adenoma (x400, ACTH-antibody, Dako). (C) Prolactin secretion in the same adenoma (x400, PRL-antibody, Dako). Positive stain is demonstrated in different cells than cells positive for ACTH. Detection of other pituitary hormones was negative.

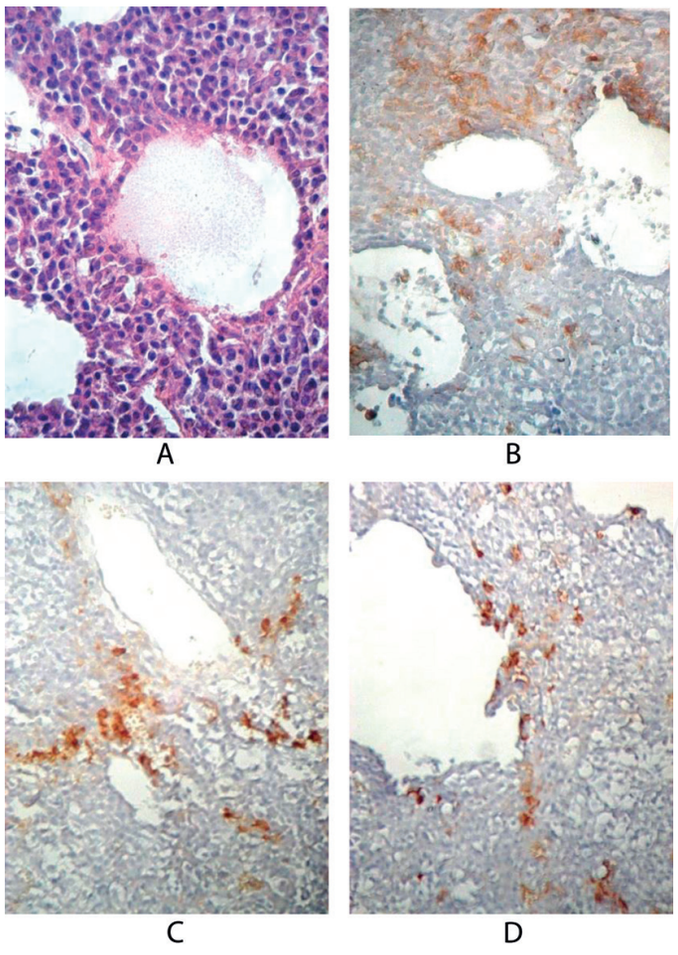

Figure 2. (A) Pituitary adenoma revealing a pseudoglandular and microcystic structure (x400, HE stain). (B). Prolactin secretion in some tumor cells (x400, PRL-antibody, Dako). (C) TSH secretion in the same tumor, apparently in different cells than prolactin secretion (x400, TSH-antibody, Dako). (D) FSH secretion in the same tumor, apparently in different cells than prolactin and TSH secretion (x400, FSH-antibody, Dako).

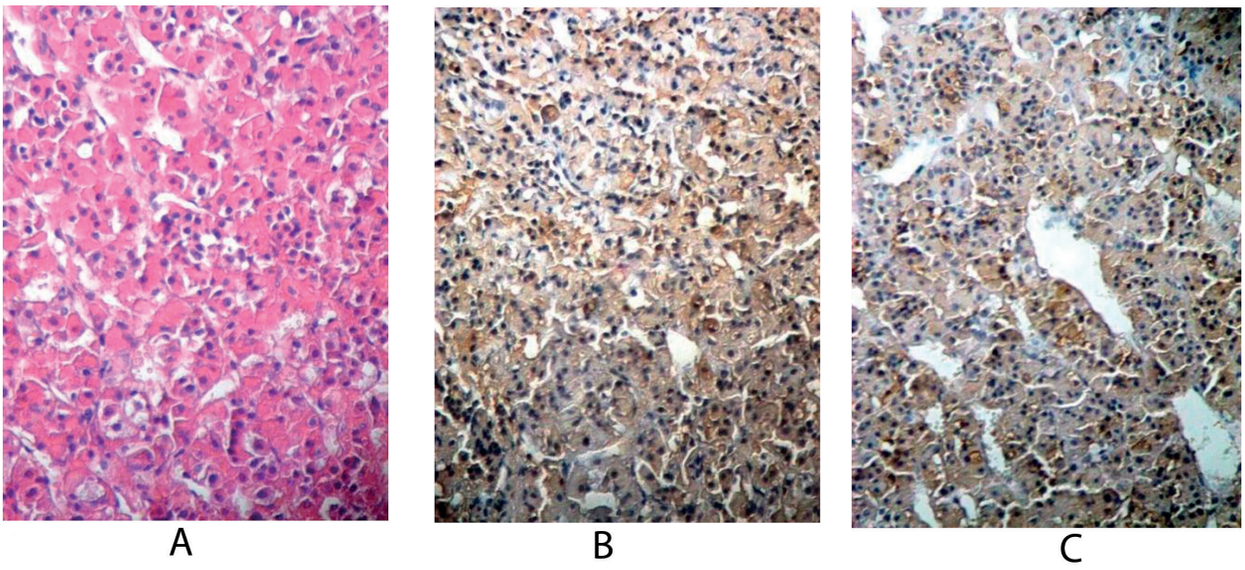

Figure 3. (A) Crooke cell adenoma (x400, HE stain). (B) ACTH secretion in the same Crooke cell adenoma (x400, ACTH-antibody, Dako). (C). Prolactin secretion in the same crook cell adenoma, apparently positive in the same cells as ACTH (x400, PRL-antibody, Dako). Detection of other pituitary hormones was negative.

Some of the secretions might remain subclinical and only detected by immunohistochemical studies.

It was noted that half of the somatotroph adenomas, particularly densely granulated adenomas, secrete other hormones; these hormones are not clinically relevant [1, 3].

A combination of hormone secretion was also reported in double pituitary adenoma base on two separate tumors on MRI imaging or histopathologic examination [5].

Pituitary adenomas with the combination of different hormone groups from the same cell lineage (GH and prolactin or FSH and LH) are relatively common, but true plurihormonal adenomas with immunoreactivities that cross the cytogenetic lineage are rare in most series as "in Refs. [5, 6, 13]."

The challenging points are:

1. How many cells that are positive for each type of hormones or pituitary transcription factors can allow the diagnosis of plurihormonal adenoma?
2. The new definition of the null cell adenoma requires the demonstration of immunonegativity for pituitary transcription factors and adenohypophyseal hormones [2, 16]; however, does the observation of rare or few positive cells for immunohistochemical markers allow to rule out the diagnosis of null cell adenoma?

4. Hormone secretion and prognosis of pituitary adenomas

Many studies tried to find out the criteria for predicting the prognosis and development of pituitary adenomas; though most of them have benign outcomes, others might have adverse outcomes and be able to invade locally, resist conventional therapy, or might recur or metastasize [2].

The following question is raised: Is any relationships exist between hormone secretion and prognosis of pituitary adenomas?

4.1. Potentially "aggressive pituitary adenoma"

Certain subtypes of pituitary adenomas are found tending to show more aggressive clinical behavior and designed by some authors as aggressive adenomas [2]; these are: sparsely granulated somatotroph adenoma (SGSA), lactotroph macroadenoma in men, Crooke cell adenoma, silent corticotroph adenoma, and plurihormonal PIT1-positive adenoma (previously called silent subtype 3 adenomas [1–3, 5]). It is also reported that pituitary adenomas found in MEN1 (multiple endocrine neoplasia type 1) tend to be plurihormonal and more aggressive [12].

4.2. "High-risk pituitary adenoma"

The defined criteria for this adenoma in the last 4th WHO classification for pituitary adenomas are, as "in Refs. [2, 3, 17]":

- Rapid growth
- Radiological invasion
- High Ki-67 proliferation index more than 3%

This adenoma tends to predict recurrence and resistance to conventional therapy [2].

It is not clear whether all potentially "aggressive pituitary adenomas" are "high-risk adenomas," as the first term depends on hormone secretion, while the second term depends on clinical and radiological data plus the immunohistochemical study for Ki-67 proliferation index. P53 is not considered as an independent risk factor [2].

A high risk adenoma with histological signs of aggressiveness is shown in **Figure 4**.

4.3. "Atypical adenoma"

The term "atypical adenoma" was previously used in the 3rd WHO classification [1]; it is defined by a high mitotic index, Ki-67 mitotic index more than 3%, and strong nuclear P53 staining. This term is no more used in the 4th classification [2], as it did not prove any utility. Atypical adenoma is replaced by the definition of "high-risk adenoma." Strong positive nuclear expression of P53 is not proved to be an independent factor of high-risk adenoma [2].

4.4. Plurihormonality and prognosis

Plurihormonal PIT1-positive adenomas are aggressive in terms of their size, growth rate, and invasiveness, with cavernous sinus invasion occurring in 67% of cases and 31% rate of recurrence [5].

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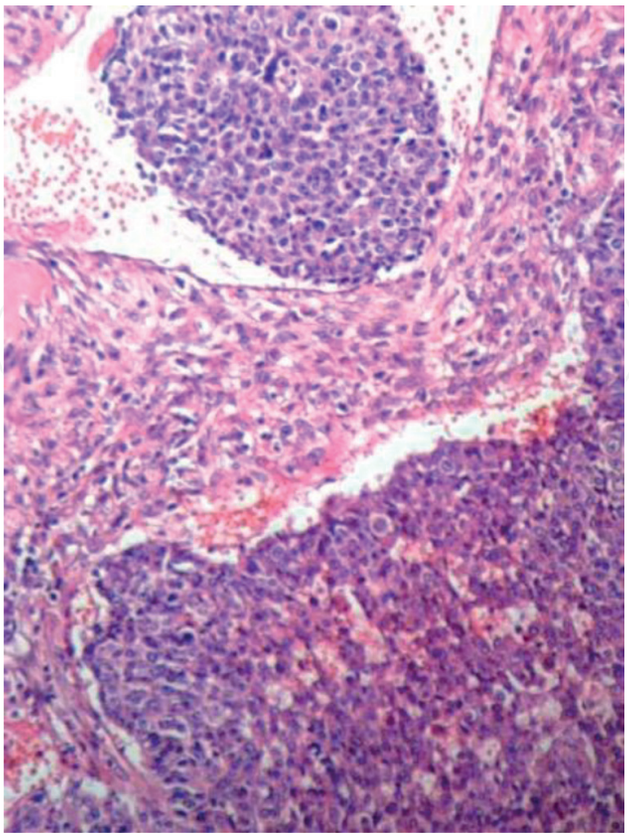

Figure 4. Aggressive and high-risk pituitary adenoma revealing vascular invasion and mitotic figures (x200, HE stain). It demonstrated immunonegativity for hormone secretion.

4.5. Pituitary carcinoma

The only conclusive criterion of malignancy is actually metastasis. The last WHO classification of pituitary adenomas strictly defined pituitary carcinoma as a tumor of adenohypophyseal cells that metastasizes craniospinally or is associated with systemic metastasis. This definition is independent of the histological appearance; as histologically, about 60% of primary tumors have features of a conventional adenoma [2, 18].

Pre-metastatic lesions and metastases can be hormonally active or clinically nonfunctioning. There are no clinical or biochemical features specific to an adenoma that will metastasize [18]. No confirmed relationship is demonstrated between non-secreting adenoma, plurihormonality, and malignancy; though, plurihormonal PIT1-positive carcinomas have also been reported [18].

4.6. Pituitary neuroendocrine tumor (PitNET)

This term is recently proposed in 2017 for pituitary adenoma by the International Pituitary Pathology Club to explain the highly variable clinical impact of pituitary adenomas on patients and the poor reproducibility of the actual predictive markers [19] though the margins are not clear between pituitary adenomas and neuroendocrine tumors.

Pituitary carcinomas are demonstrated positive for neuroendocrine differentiation like synaptophysin and chromogranin A [18].

5. Necessity of hormone detection by immunohistochemical studies

5.1. Questions frequently raised when we have a case of pituitary adenoma

Pathologists and clinicians might ask the following questions:

1. Is it necessary to make histological study to every pituitary adenoma?
2. Is it necessary to demonstrate hormonal production in all pituitary adenomas studied by pathologists?
3. How many antibodies should a pathologist use to study this adenoma?
4. Which antibodies have clinical utility for treatment and prognostic prediction?
5. Can we predict the aggressiveness of a pituitary adenoma before that it becomes clinically and radiologically aggressive?

5.2. Importance of immunohistochemical studies

We might find answers on the previous questions in the following findings:

- Classification of pituitary adenomas requires morphological and hormonal immunohistochemical assessment [2, 3].
- Nonfunctional adenomas, with no hormone detection in the serum, are not necessarily nonproducing adenomas. Detection of hormonal production by immunostaining leads to term them "silent adenomas" [2, 3]. Some authors recently proposed to term them "poorly differentiated Pit-1 lineage adenomas" [20].
- Immunostaining is important to diagnose some of the potentially "aggressive adenomas" subtypes as mentioned before.
- Detection of PIT1 and hormonal production is important for the diagnosis of plurihormonal PIT1-positive pituitary adenomas (previously called silent subtype 3 adenomas) that are considered as potentially "aggressive adenoma" [2, 5].
- Detection of the somatostatin receptor by immunohistochemistry may be a useful predictor of treatment response, as SGSAs are less responsive to somatostatin antagonists and may require treatment with the GH receptor antagonist pegvisomant [21].
- Demonstration of immunonegativity for hormones and transcription factors, especially Pit-1, is important for the differential diagnosis between silent adenomas and null cell adenoma, as the latter has good prognosis. Some silent adenomas, notably silent corticotroph adenoma and plurihormonal PIT1-positive adenoma (previously called silent subtype 3 adenomas), are considered potentially "aggressive adenomas" [2, 17, 22].

- Demonstration of NSE, chromogranin A and synaptophysin helps to diagnose PitNET and might predict more aggressive potential even before that the tumor comes clinically and radiologically aggressive.

5.3. Recommended antibodies for the diagnosis and prediction

It is important to demonstrate hormone production, transcription factors for functional differentiation, and proliferation index that indicate prediction. Practically, the following immunohistochemical stains are recommended in studying a pituitary adenoma as they cover wide area of diagnosis and prediction:

- GH, prolactin, TSH-beta, ACTH, FSH-beta, LH-beta, and alpha-SU to make an accurate classification of the studied pituitary adenoma.
- Pit-1 and TPIT transcription factors and ER-alpha are recommended when there is immunonegativity for pituitary hormones, to rule out potentially aggressive silent adenomas. SF1, the transcription factor for gonadotroph cell lineage does not seem to have prognostic importance, as gonadotroph adenomas are usually not aggressive.
- Ki-67 proliferation index, for the demonstration of "high-risk adenomas."
- Chromogranin A and synaptophysin diagnose PitNET that might predict more aggressive behavior.
- P53 is not an independent risk factor of aggressiveness; so it is not necessary to demonstrate it.

6. Conclusions

Immunohistochemical studies have increasing importance in pituitary adenomas. Demonstration of hormones, some transcription factors and cofactors for functional differentiation, and proliferation index have important roles in the classification, prediction, and treatment of these adenomas, as demonstration of neuroendocrine differentiation.

Conflict of interest

I declare that there is no "conflict of interest" in this chapter.

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References

[1] Lloyd RV, Kovacs K, Young WF Jr, Farrell W, Asa SL, et al. Pituitary tumors: Introduction. In: Delellis RA, Lloyd RV, Heitz PU, Eng C, editors. World Health Organization Classification of Tumors. Pathology and Genetics of Tumors of Endocrine Organs. 3rd ed. Lyon: IARC Press; 2004

[2] Osamura RY, Lopes MBS, Grossman A, Kontogeorgos G, Trouillas J. Introduction. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J. editors. World Health Organization Classification of Tumors. WHO Classification of Tumours of Endocrine Organs. 4th ed. IARC Press: Lyon 2017. pp. 13

[3] Osamura RY, Grossman A, Korbonits M, Kovacs K, Lopes MBS, et al. Pituitary adenoma. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization Classification of Tumors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC Press; 2017. pp. 14-18

[4] Nishioka H, Inoshita N, Mete O, Asa SL, Hayashi K, et al. The complementary role of transcription factors in the accurate diagnosis of clinically nonfunctioning pituitary adenomas. Endocrine Pathology. 2015;**26**:349-355. DOI: 10.1007/s12022-015-9398-z

[5] Kontogeorgos G, Kovacs K, Lloyd RV, Righi A. Plurihormonal and double adenoma. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization Classification of Tumors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC Press; 2017. pp. 39-40

[6] Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. European Journal of Endocrinology. 2007;**156**(2): 203-216. DOI: 10.1530/eje.1.02326

[7] Al Khani R. Plurihormonal secretion in pituitary adenomas: Immunohistological study of 100 cases. JABMS (Journal of the Arab Board of Medical Specializations). 2002;**4**(4): 89-95E. ISSN 1561-0217

[8] Kwinta BM, Krzyżewski RM, Kliś K, Adamek D. Quantitative immunohistochemical assessment of clinically non-functioning pituitary adenomas. Medical Research Journal. 2017;**2**(4):147-151. DOI: 10.5603/MRJ.2017.0020

[9] Rajendran R, Naik S, Sandeman DD, Nasruddin AB. Pasireotide therapy in a rare and unusual case of plurihormonal pituitary macroadenoma. Endocrinology, Diabetes & Metabolism Case Reports. 2013;**2013**:130026. DOI: 10.1530/EDM-13-0026

[10] Rasul FT, Jaunmuktane Z, Khan AA, Phadke R, Powell M. Plurihormonal pituitary adenoma with concomitant adrenocorticotropic hormone (ACTH) and growth hormone (GH) secretion: A report of two cases and review of the literature. Acta Neurochirurgica. 2014;**156**(1):141-146. DOI: 10.1007/s00701-013-1890-y

[11] Roca E, Mattogno PP, Porcelli T, Poliani L, Belotti F, et al. Plurihormonal ACTH-GH pituitary adenoma: Case report and systematic literature review. World Neurosurgery. 2018;**114**:e158-e164. DOI: 10.1016/j.wneu.2018.02.120

[12] Uraki S, Ariyasu H, Doi A, Furuta H, Nishi M, et al. Hypersecretion of ACTH and PRL from pituitary adenoma in MEN1, adequately managed by medical therapy. Endocrinology, Diabetes & Metabolism Case Reports. 2017;**2017**:17-0027. Published online 2017 Apr 6. DOI: 10.1530/EDM-17-0027

[13] Kunasegaran S, Croxson MS, Holdaway I, Murphy R. An unusual case of Cushing's syndrome due to bihormonal ACTH–prolactin secreting pituitary macroadenoma with rapid response to cabergoline. https://www.ncbi.nlm.nih.gov/pubmed/28784879. BMJ case reports. BMJ Case Reports. 2017 Aug 7;2017. DOI: 10.1136/bcr-2017-219921

[14] Batisse Lignier M, Maqdasy S, Mestre B, Roche B, Chazal J, Tauveron I. An unusual plurihormonal pituitary adenoma. In: 15th International & 14th European Congress of Endocrinology; 05-09 May 2012; Florence, Italy. Endocrine Abstracts; 2012; 29. p. 1540

[15] Luk CT, Kovacs K, Rotondo F, Horvath E, Cusimano M, Booth GL. Plurihormonal pituitary adenoma immunoreactive for thyroid-stimulating hormone, growth hormone, follicle-stimulating hormone, and prolactin. Endocrine Practice. 2012;**18**(5):e121-e126. DOI: 10.4158/EP12033.CR

[16] Mete O, Lopes MB. Overview of the 2017 WHO Classification of Pituitary Tumors. Endocrine Pathology. 2017;**28**(3):228-243. DOI: 10.1007/s12022-017-9498-z

[17] Nishioka H, Inoshita N. New WHO classification of pituitary adenomas (4th edition): Assessment of pituitary transcription factors and the prognostic histological factors. Brain Tumor Pathology. 2018;**35**(2):57-61. DOI: 10.1007/s10014-017-0307-7

[18] Roncaroli F, Kovacs K, Lloyd RV, Matsuno A, Righi A. Pituitary carcinoma. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization Classification of Tumors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC Press; 2017. pp. 41-44

[19] Asa SL, Casar-Borota O, Chanson P, Delgrange E, Earls P, et al. From pituitary adenoma to pituitary neuroendocrine tumor (PitNET): An International Pituitary Pathology Club proposal. Endocrine-Related Cancer. 2017;**24**(4):C5-C8. DOI: 10.1530/ERC-17-0004

[20] Mete O, Gomez-Hernandez K, Kucharczyk W, Ridout R, Zadeh G, et al. Silent subtype 3 pituitary adenomas are not always silent and represent poorly differentiated monomorphous plurihormonal Pit-1 lineage adenomas. Modern Pathology. 2016;**29**(2):131-142. DOI: 10.1038/modpathol.2015.151

[21] Mete O, Korbonits M, Osamura RY, Trouillas J, Yamada S. Somatotroph adenoma. In: Lloyd RV, Osamura RY, Klöppel G, Rosai J, editors. World Health Organization Classification of Tumors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: IARC Press; 2017. pp. 19-23

[22] Lee JC, Pekmezci M, Lavezo JL, Vogel H, Katznelson L, et al. Utility of Pit-1 immunostaining in distinguishing pituitary adenomas of primitive differentiation from null cell adenomas. Endocrine Pathology. 2017;**28**(4):287-292. DOI: 10.1007/s12022-017-9503-6

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